REMARKS

I. Status of the Claims

Claims 1-70 are pending in the application. Claims 57-59, 61 and 62 are withdrawn from consideration, and claims 9, 40 and 45 have been canceled. Thus, claims 1-8, 10-25, 26-39, 41-44, 46-56, 60 and 63-70 are pending, under examination and stand rejected. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Summary of Interview

On August 5, 2003, applicants' representative conducted a telephonic interview with Examiner Schnizer. Applicants are appreciate of the examiner's time and, though no agreement was reached, applicants believe that the remaining issues were substantially clarified.

II. Objections to the Specification and Claims

The objections to the specification are noted. Amendments have been provided addressing each of the objections. Claims 1 and 11 have been amended to insert "a" and "an," respectively, at the indicated places.

III. Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 2-5, 10-33, 35-37, 53-56, 60 and 63-70 are rejected under the second paragraph of §112 as allegedly indefinite. The individual rejections are addressed below:

Claims 2-5 and 26-33. The examiner has pointed out that "said epithelial tissue" lacks antecedent basis. Claims 2 and 26 have been amended to obviate the rejection.

Claims 10-33, 36 and 37. The rejected claims depend from canceled claim 9. Appropriate amendments have been provided, or the claim canceled.

Claims 26-31. The examiner argues that these claims are ambiguous in not specifying when the viral infection takes place with respect to the increase of transepithelial permeability. A clarifying amendment is offered.

Claims 35 and 36 (believed to be claims 34 and 35). These claims are said to lack antecedent basis for the term "said proliferative factor." Applicants traverse. Both claims depend from claim 7, which contains the term in question.

Claims 53-56, 60 and 63-67. The claims are rejected as lacking antecedent basis for "said therapeutic polypeptide." An amendment to claim 53 is offered, thereby obviating the rejection.

IV. Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1-8, 10-37, 53-56, 60, 63-67 and 70 stand rejected as allegedly lacking an enabling disclosure. The examiner makes a number of distinct rejections, each of which are addressed separately below.

Claims 1-8 and 10-37. The examiner has objected to the scope of the claims, primarily in the context of "viruses" and "permeabilizing agents." Applicants traverse, but in the interest of advancing the prosecution, the claims have been limited to use of "viral vectors" and "hypotonic solutions and/or ion chelators."

Claims 26-34. The examiner states that the present invention functions only during a period of tissue permeabilization, which period is transient. Hence, it is argued that the claims should be limited to administration of viral vectors to permeabilized tissue. Applicants traverse,

as the case law clearly permits the specification to provide the operating parameters for a claimed process. In *Ex parte Jackson*, 218 USPQ 804 (CCPA 1982), claims were rejected under the second paragraph of §112 as being incomplete for failing to recite various process parameters. In reversing the examiner, the Board stated that

> It is by now well established that it is the function of the descriptive portion of the specification and not that of the claims to set forth operable proportions and similar process parameters and the claims are not rendered indefinite by the absence of the recitation of such limitations. *In re Fuetterer*, ... 138 USPQ 217 (CCPA 1963); *In re Johnson*, ... 194 USPQ 187 (CCPA 1977).

Jackson at 806. Thus, the failure of the claims to recite a detailed comparison step was not an appropriate grounds for rejection. As stated in *Johnson*, "one does not look to claims to find out how to practice the invention they define, but to the specification. *In re Roberts*, ... 176 USPQ 313, 315 (CCPA 1973) ...." *Johnson* at 195.

However, in the interest of advancing the prosecution, applicants have amended the claims as suggested by the examiner.

Claims 48 and 49. The examiner has rejected the claims as overly broad with respect to the type of receptor redistribution and the type of tissue permeabilization. Applicants traverse, but in the interest of advancing the prosecution, the claims have been amended to recite basolateral-to-apical redistribution as well as specific tissue permeabilizing agents.

Claim 70. The examiner objects to the term "transforming" as it is applied to eukaryotic cells. Applicants traverse, but in the interest of advancing the prosecution, an amendment has been offered making the suggested change from "transforming" to "transducing."

Claims 53-56, 60 and 63-67. The examiner once again rejects the claims as lacking enablement based on the "treatment" of cystic fibrosis via gene therapy. The examiner also

discusses "generic claims embracing treatment of any and all epithelial tissues diseases." However, as the election of species requirement (cystic fibrosis; hypotonic solution and/or ion chelator) excludes such other treatments, a discussion of those issues is premature.

At one level, the issue is that the term "treatment" includes a variety of results ranging from expression of the CFTR transporter to a complete cure. This argument is unavailing. Even expression of the CFTR transporter "embraces" a cure, yet it is inconceivable that such a recitation would be rejected on this ground. All that is required for enablement is that a "treatment" be effected, and no specific result is required.

At another level, the examiner continues to challenge the therapeutic benefit of expressing the CFTR receptor *in vivo*, though noting that U.S. Patent 5,962,429 contains claims to expressing a CFTR transgene in airway epithelia of a patient. However, one must ask what utility and enablement these claims rely upon for patentability, if not *in vivo* therapy. Applicants also point to U.S. Patent 5,670,488, which contains a claim (claim 13) directed to the delivery of a CFTR gene to epithelial cells of a cystic fibrosis patient using a particular adenovirus vector, raising a similar question there. Regardless, the PTO has conceded ***some*** utility and enablement for these claims.

Thus, applicants will not endeavor to rehash the discussion at pages 14-20 of the office action as the issues contained therein have been actively debated for the past 18 months. Rather, applicants submit that the present record is such that one need no longer argue over whether CFTR gene therapy is enabled. The '429 and '488 patents show that there is both utility and enablement for such endeavors, and applicants here should not be required to "reinvent the wheel" in this regard. In fact, the PTO should be estopped from arguing that CFTR gene therapy is not workable, since it has issued two U.S. patents indicating that it ***is*** workable. Yet effectively this is what the present action argues. Of course, each application is judged on its own merits, but so long as

applicants' specification is not defective in presenting the proper vectors and methods of administration, there is no merit in arguing that which has previously been decided in favor of applicants.

In order to make the factual correlation with the '429 and '488 patents complete, applicants have amended claim 53 to track the language of these issued patents:

> 53. A method of providing a cystic fibrosis transmembrane conductance regulator (CFTR) protein to airway epithelial tissue in a subject with cystic fibrosis comprising:
>
> (a) providing a packaged viral vector comprising a polynucleotide encoding said CFTR protein;
> (b) increasing the permeability of the epithelial tissue by contacting said tissue with a hypotonic solution and/or an ion chelator; and
> (c) contacting cells of said epithelial tissue with said packaged viral vector under conditions permitting the uptake of said packaged viral vector by said cells and expression of said CFTR protein therein,
>
> whereby expression of said CFTR protein provides said CFTR protein to said epithelial tissue.

Thus, applicants submit that unless (a) there is a ***substantive*** difference between this claim and those in the '429 and '488 patents that would impact enablement, or (b) there is a ***substantive*** difference in the enabling quality of the specification, this claim should not be rejected on enablement grounds.

In sum, all of the grounds for rejection under 35 U.S.C. §112, first paragraph have been addressed by amendments and rebuttal argument, as set forth above. Reconsideration and withdrawal of the rejections is thus respectfully requested.

V. Rejections Under 35 U.S.C. §102(b)

A. Kaplan et al. – claims 1-5, 13, 14, 26-28, 30 and 48-50

Kaplan is said to teach a method of increasing replication deficient adenoviral transduction and expression of a human transgene in alveoli, bronchial, and tracheal epithelium by nasal instillation of adenoviruses and polylysine. Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled or amended to recite only the use of ion chelators or hypotonic solutions. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

B. Kleeberger et al. – claims 1-5, 22, 23, 48 and 49

Kleeberger is said to teach a method of increasing permeability in airway epithelia by forcing rats to breath ozone gas. Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled or amended to recite only the use of ion chelators or hypotonic solutions. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

C. Johnson et al. – claims 1, 2, 4, 6, 7, 26, 27,30 and 48-52

Johnson is said to teach a method of delivering retroviral vectors to tracheal cells *in vivo* and thereby causing expression of a non-viral reporter gene, and where epithelial tight junction permeability and proliferation were increased by treatment with sulfur dioxide gas prior to infection. Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled or amended to recite only the use of ion chelators or hypotonic solutions. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

D. Welsh et al. (patent) – claims 1, 2, 13, 14, 26-30, 32, 33, 36, 37, 48, 50, 53-56, 60 and 63-65

Welsh is said to teach a method of providing a cystic fibrosis transmembrane conductance regulator to airway epithelial cells of a CF patient comprising combining cationic polypeptide polymers with adenoviral particles containing a CFTR transgene, where the transgene is expressed and a functional chloride channel is produced in the cells. Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled or amended to recite only the use of ion chelators or hypotonic solutions. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

E. Olsen et al. – 1, 2, 4, 13, 26, 27, 30-33, 35, 37-39, 41-44, 46-50 and 52

Olsen is said to teach a method of transducing a cystic fibrosis tracheal epithelial cell line with replication-deficient retroviruses. The transduction efficiency was said to be improved by the presence of cationic polypeptides. Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled or amended to recite only the use of ion chelators or hypotonic solutions. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

F. Katkin et al. – claims 1, 5, 26, 27, 30, 37 and 48-50

Katkin is said to teach a method of infecting alveolar epithelia with a replication defective adenoviral vector, delivered topically to lung epithelium in 10% glycerol. Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled or

amended to recite only the use of ion chelators or hypotonic solutions. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

G. Marano et al. – 1, 6-8, 24, 25, 35, 48 and 49

Marano is said to teach a method of increasing transepithelial permeability by treatment of epithelia with TNF-α. Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled or amended to recite only the use of ion chelators or hypotonic solutions. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

H. Cornetta et al. – 1, 7, 8, 13, 26-31, 35, 37 and 48-52

Cornetta is said to teach a method of increasing replication-deficient retroviral transduction of epithelial cells by exposure to protamine. Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled or amended to recite only the use of ion chelators or hypotonic solutions. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

I. Debs et al. – 1, 7, 34, 36, 37, 48 and 49

Debs is said to teach a method of aerosol deliver of TNF-α to rat lung epithelium. Applicants traverse, but in the interest of advancing the prosecution, the claims have been amended to recite only the use of ion chelators or hypotonic solutions. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

J. Jongeneel et al. – claims 1, 10-12, 48, 49 and 68

Jongeneel is said to teach a method of permeabilizing epithelial cells by shock with a hypotonic solution comprising EGTA. Applicants traverse, but in the interest of advancing the prosecution, the claims have been amended to recite the active step of viral infection or *in vitro* administration. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

K. Tomita et al. – claims 1, 11, 12, 48 and 49

Tomita is cited as teaching a method of permeabilizing cells with exposure to EDTA. Applicants traverse, but in the interest of advancing the prosecution, the claims have been amended to recite the active step of viral infection or *in vitro* administration. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

L. Zegarra-Moran et al. – claims 1, 11, 12, 48 and 49

Zegarra-Moran is said to teach a method of permeabilizing epithelial cells by exposure to BAPTA. Applicants traverse, but in the interest of advancing the prosecution, the claims have been amended to recite the active step of viral infection or *in vitro* administration. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

M. Meza et al. – claims 1, 11, 12, 16, 17, 48 and 49

Meza is said to teach a method permeabilizing epithelial cells by exposure to cytochalasin B or EGTA. Applicants traverse, but in the interest of advancing the prosecution, the claims have been amended to recite the active step of viral infection or *in vitro*

administration. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

N. McEwan et al. – claims 1, 13, 14, 48 and 49

McEwan is said to teach a method of increasing paracellular permeability to epithelial tissue by treatment with polylysine. Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled or amended to recite the active step of viral infection, as well as being limited to use of hypotonic solutions or ion chelators. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

O. Arcasoy et al. – claims 1, 13, 14, 26, 27, 30, 32, 33 and 48-50

Arcasoy is said to teach a method of increasing adenoviral transduction and expression of a transgene in diseased epithelial cells *in vitro* by exposing the cells to polylysine. Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled or amended to recite only the use of ion chelators or hypotonic solutions. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

P. Wong et al. – claims 1, 15, 48 and 49

Wong is said to teach a method of increasing paracellular transepithelial permeability by treatment of epithelia with an occludin peptide. Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled or amended to recite the active step of viral infection, as well as being limited to use of hypotonic solutions or ion chelators. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

Q. Yap et al. – claims 1, 17, 48 and 49

Yap is said to teaches a method of increasing paracellular transepithelial permeability by treatment of epithelia with colchicine. Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled or amended to recite only the use of hypotonic solutions or ion chelators. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

R. Richardson et al. – claims 1, 18, 48 and 49

Richardson is said to teach a method of increasing transepithelial permeability in tracheal epithelium by treatment of the epithelium with ether. Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled or amended to recite only the use of hypotonic solutions or ion chelators. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

S. Hashimoto et al. – claims 1, 19, 20, 48 and 49

Hashimoto is said to teach a method of increasing epithelial tight junction permeability by treatment of the epithelium with capsianoside. Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled or amended to recite only the use of hypotonic solutions or ion chelators. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

T. Li et al. – claims 1, 21, 48 and 49

Li is said to teach a method of increasing epithelial tight junction permeability by treatment of the epithelium with FCCP. Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled or amended to recite the active step of viral infection, as well as being limited to use of hypotonic solutions or ion chelators. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

U. Welsh et al. (journal) – 1, 22, 23, 48 and 49

Welsh is said to teach a method of increasing paracellular transepithelial permeability by treatment of epithelial with hydrogen peroxide. Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled or amended to recite only the use of hypotonic solutions or ion chelators.

V. Flasshove et al. – claims 38, 39, 41-44, 46 and 47

Flasshove is said to teach a composition comprising a solution of retroviruses, fetal bovine serum, protamine and IL-1. Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled.

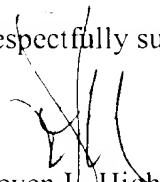
W. Wunderlich et al. – claims 68 and 69

Wunderlich is said to teach a suspension of viral particles in a hypotonic solution of 1 mM EGTA. Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled.

V. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. The examiner is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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